Regular review

HIV infection in children

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HIV has transformed paediatric practice in developing countries. A specialty that once dealt mainly with acute illnesses is now consumed, in many settings, with managing chronically ill and dying children. Last year, 600 000 children were newly infected with HIV, over 90% in sub-Saharan Africa and almost all having acquired the virus by vertical transmission, from mother to child.[1] The statistics do not adequately portray the suffering and disrupted lives of the most vulnerable of the world's population.

The HIV pandemic has eroded many of the hard earned gains made in reducing infant and child mortality. The United Nations Program on HIV and AIDS (UNAIDS) recently reported that, by 2010, a doubling in child mortality is expected in regions with a high prevalence of infection. Globally, the number of orphans from AIDS will increase from the current 13.2 million to 44 million by 2010.[2] Already, one child in 10 is an orphan in some countries. Finding appropriate responses to this crisis must rank as the single most important global challenge to child health in the next decade.

This article reviews advances in preventing vertical transmission, antiretroviral treatment, and vaccine development, and we attempt to predict future developments.

Summary points

- HIV infection and AIDS have severely disrupted child health services in many developing countries
- Efforts to prevent viral transmission form mother to child are inadequate in resource poor settings
- The choice between breast feeding and feeding with formula milk remains controversial
- An effective AIDS vaccine can be expected in the next 10 years
- New antiretroviral treatments and innovative treatment strategies continue to be developed
- A focus beyond education and promoting the use of condoms is required in poor countries

Methods

The review is based on a Medline search of original papers and reviews, unpublished material, presentations and abstracts from recent scientific meetings, information obtained from the internet, and personal communications with scientists and clinicians.

Course of HIV infection in children

Considerable progress has been made in understanding the natural course of HIV infection in children. Infected children differ from infected adults in several ways. Firstly, the disease progresses much more rapidly in children; secondly, children have higher viral loads than those usually seen in adults; thirdly, children have recurrent invasive bacterial infections more often[3]; and, finally, opportunistic infections often present as primary diseases with a more aggressive course because of the lack of prior immunity. Despite these differences, children's cellular responses to HIV are similar to those of adults, and they respond almost as well to aggressive, multidrug antiretroviral regimens.

Prevention strategies to reduce vertical transmission

Reducing vertical transmission from mother to child is a vital component of any HIV prevention strategy, particularly in resource poor countries, where up to 40% of pregnant women are infected with HIV and 25-48% of their children inherit the disease.[4] In populations where breast feeding is uncommon most transmission (about 65%) occurs during the intrapartum period, while in communities where breast feeding is common postpartum transmission contributes from a third to a half of vertically transmitted infections.

Prophylactic antiretroviral treatment

Antiretroviral treatment reduces vertical transmission by decreasing maternal viral load and by providing prophylaxis to the infant before and after exposure. It is still unclear whether antiretroviral treatment is best targeted at the antenatal, intrapartum, or postpartum period. Recent work suggests that longer antenatal treatment with zidovudine (from 28 weeks' gestation onwards) is better than a shorter course (from 36

Worldwide numbers of children (aged <15 years) estimated to have been orphaned by AIDS at end of 1999 (total 13.2 million) and those estimated to be living with HIV infection or AIDS at end of 2000 (total 1.4 million). (Adapted from Joint United Nations Programme on HIV/AIDS (UNAIDS), World Health Organization. Report on the global HIV/AIDS epidemic. Graphics epidemic update—December 2000 (www.unaids.org/wac/2000/wad00/files/wad2000Master/index.htm)

weeks) and that the former strategy combined with just three days of zidovudine treatment for the infant may be as effective as a six week course of postnatal zidovudine.[5] The use of combination antiretroviral treatment that decreases maternal viral loads to undetectable levels is now routine in many developed countries and reduces HIV transmission rates to less than 2% (with or without elective caesarean deliveries).[6]

Currently, 95% of vertical transmission occurs in developing countries. The challenge in these settings is to find the shortest, most cost effective, and practical treatment regimen. Nevirapine, a non-nucleoside reverse transcriptase inhibitor, is presently favoured; administration to the mother at the time of delivery and one dose given to the baby within 72 hours of birth results in a 47% reduction in viral transmission.[7] It is relatively cheap at $4 (£2·50) for the course, and its manufacturer has agreed to provide it at no cost to prevent vertical transmission in some developing nations. Despite this, and a recommendation from the World Health Organization and UNAIDS that the prevention of vertical transmission of HIV be included in a minimum standard of care, most governments have been slow in responding. Excuses cited include difficulties with providing the prerequisite antenatal HIV screening, counselling, and distribution services and exaggerated fears about drug toxicity and resistance.

Although no substantial immunological, growth, developmental, carcinogenic, or other adverse effects have been related to perinatal exposure to zidovudine,[8] concerns remain about the toxicity of antiretroviral treatment in pregnancy, including potential teratogenicity, mutagenicity, carcinogenicity, reproductive effects, and mitochondrial toxicity. Current data indicate that the benefits of antiretroviral treatment to prevent perinatal transmission of HIV far outweigh any potential harm. Future strategies in poorer settings may include regular administration of antiretroviral treatment to infants while breast feeding continues (such as a weekly dose of nevirapine) or providing combination antiretroviral treatment to mothers for the same period.

Interventions during pregnancy and delivery

Elective caesarean delivery reduces HIV transmission by over half compared with other modes of delivery, with simultaneous administration of zidovudine providing additional benefit (85% reduction).[9] However, this is an inappropriate intervention in resource poor settings because of staff and cost constraints, and possible increases in postoperative complications in HIV infected women. Disappointing results have been obtained using simpler and cheaper interventions to prevent vertical transmission. Cleansing the vagina with chlorhexidine during labour has proved ineffective in African studies, although lavage before membranes are ruptured might reduce transmission.[10 11] Various combinations of micronutrient supplementation during pregnancy and post partum have also failed to reduce HIV transmission.[12] Vitamin A supplementation for pregnant women is similarly ineffective.[12 13]

Interruption of breast milk transmission

The debate over breast feeding versus formula feeding in resource poor settings continues. Recent research on three key issues may influence future policy. One critical question is whether breast feeding is associated with adverse outcomes for mother and infant. This seems to be the case. A Kenyan study comparing breast and formula feeding cohorts found, not surprisingly, that at 24 months more breastfed children had

acquired HIV (36.7% *v* 20.5%). However, mortality was not significantly different in the two groups.[14] Nevertheless, mortality after 24 months is likely to be greater in the breastfed group because of the higher HIV prevalence. Of greater concern was the effect of breast feeding on the mothers' health, with this cohort having a 3.2 times higher mortality. Children whose mothers died had an eightfold increased risk of dying themselves.[15]

A second issue is whether the pattern of breast feeding influences transmission. Exclusive breast feeding for the first three months of life may be as safe as formula feeding and much safer than mixed feeding in preventing viral transmission,[16] but this finding needs to be confirmed. Thirdly, the benefit of providing perinatal antiretroviral treatment in settings where breast feeding is the norm or favoured has been questioned. Current evidence is conflicting. One study showed no reduction in overall HIV transmission at 18 months,[17] but two others found a 42% and 28% reduction in transmission at ages 12 and 24 months respectively despite continued breast feeding.[18 19] While further research may assist in formulating policy about optimal feeding choices, it is unlikely that universal consensus will be ever be attained because of the variety of settings and situations that have to be covered and the passionate beliefs of the antagonists.

Vaccination

Progress towards an HIV vaccine has been slow, partly because of the lack of a financial incentive and poor political commitment. Vaccine research has progressed from its early focus on HIV envelope proteins and the role of antibodies to increased attention on the importance of cytotoxic T cells. The challenges in developing safe and effective vaccines are daunting—including dealing with multiple HIV clades, or subtypes, and "recombinants" (mutations containing characteristics of two or more subtypes). Scientists, however, remain optimistic. Novel ways of presenting HIV proteins to the immune system continue to be designed and tested, as do new vaccine formulations of antigen and adjuvant.

There is no documented case of the immune system protecting a child from HIV infection or disease. However, intriguing examples of multiply exposed adults who remain seronegative long term and do not progress to AIDS suggest that partial natural protection occasionally occurs. There is further cause for hope in that infection with HIV-2, a much less pathogenic virus than HIV-1, protects some individuals from HIV-1 infection later. In primates vaccination against simian immunodeficiency virus (SIV) has succeeded in protecting against both virus infected cells and free virus particles and against systemic and mucosal infection.

At present, only one vaccine concept is being tested in phase III (efficacy) trials in adults. However, at least six of the more than 50 phase I and II trials of candidate vaccines are specifically targeting children or vertical transmission. An effective AIDS vaccine may be developed within the next 10 years, but it is debatable whether it will be affordable to those most in need of it. The ideal vaccine would probably have a combination effect to stimulate the strongest, most durable, and yet most specific range of cellular immune responses to HIV. Maternal and neonatal immunisation offer the best prospects for reducing vertical transmission. A combination of both passive (immunoglobulin) and active immunisation of the neonate, as is used to prevent hepatitis B when mothers are carriers, may be most efficacious.

Routine childhood vaccinations have an important role in preventing common illnesses that affect HIV infected children. These children show few adverse reactions to routine vaccinations, including live vaccines. Of concern, however, is the reduced effectiveness of newer conjugate vaccines, such as those against *Haemophilus influenzae* and pneumococcus, in these children (S Madhi, unpublished observations). Children can achieve or re-achieve detectable levels of protective antibodies after revaccination during combination antiretroviral treatment.

Antiretroviral treatment

Antiretroviral treatment has dramatically reduced morbidity and mortality in both adults and children infected with HIV. Treatment options for children have grown considerably over the past few years. To date, the US Food and Drug Administration has approved 11 different antiretroviral treatments in children. Two classes of drugs target the reverse transcriptase enzyme, while a third class, the protease inhibitors, targets the viral protease enzyme. Together, the drugs are able to suppress plasma HIV concentrations below the level of detection.

AP PHOTO/DAVID LONGSTREATH

Six month old Roath Chamrouen, one of the children abandoned at birth infected with HIV who are cared for at the Phnom Penh Nutrition Center in Cambodia

For patients in whom previous treatments have failed, new drugs that target the attachment, binding, or entry of HIV to the CD4 cell may offer renewed hope. For example, T-20, a fusion inhibitor, has shown promise in paediatric clinical trials.[20] Other novel targets are the viral integrase enzyme or its nucleocapsid protein. To reduce toxicity and costs, future research may attempt to establish the ideal timing for starting treatment and the value of structured treatment interruptions (cycles of treatment in order to enhance specific immunity to HIV). Future treatments will almost certainly favour immune modulation; viable options include the exogenous administration of cytokines, which promote immune reconstitution by T cell regeneration, and therapeutic administration of vaccine.

Antiretroviral treatment has several limitations—it fails to eliminate latently infected cells (resting memory CD4 cells) and to completely suppress viral replication. Despite a good initial response, viral breakthrough and treatment failure often occur. Viral resistance to drugs is increasing.[21] Most importantly, it remains unaffordable for 95% of infected adults and children worldwide. Even if the cost issue was resolved, the complexity of the various regimens and the many side effects make adherence difficult, and the infrastructure needed to support antiretroviral treatment limits its widespread availability.

Rather than rejecting antiretroviral treatment outright because of this, alternative and innovative treatment options have to be found for resource poor settings. While the optimal timing of treatment in these settings has not been studied, starting treatment in the later stages of disease makes practical sense. As in the successful approach used in Haitian adults,[22] antiretroviral treatment could be prescribed to children based on easily observed clinical signs and symptoms rather than sophisticated laboratory tests, such as CD4 cell counts and viral load. New, fixed dose combinations, which combine several antiretroviral drugs in a single tablet, can help make treatment easier and thus can help forestall the development of resistance. For monitoring treatment, alternative technologies for measuring CD4 cell counts and viral load exist that are less expensive than those customarily used in developed countries.[23] For example, the simpler and cheaper heat denatured p24 assay for viral load compares favourably with conventional reverse transcriptase testing.[24] Clinicians should, nevertheless, beware of opting for "cheaper" treatment alternatives such as monotherapy, suboptimal antiretroviral treatment regimens or doses, or short periods of treatment as they are generally ineffective and induce drug resistance.

Future developments

The key to preventing HIV infection in children clearly lies in preventing their parents from acquiring the disease. Unfortunately, except for isolated successes such as in Uganda and Thailand (associated with sex education and increased condom use), there is little hope that the expansion of the pandemic will be halted soon. Much more effort needs to be directed at the sociocultural and economic aspects of preventing the spread of HIV and in linking them to the biomedical approaches highlighted in this paper.

Additional educational resources

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Online resources

AIDS Education Global Information System (AEGIS)—www.aegis.com
Self proclaimed largest website on AIDS and HIV in the world, updated hourly

The Body—http://thebody.org/
Excellent, comprehensive resource on HIV and AIDS, also offering a free "Ask the experts" service

HIV/AIDS Treatment Information Service (ATIS)—www.hivatis.org/
Contains current US treatment guidelines, including paediatric and perinatal guidelines

PENTA (Paediatric European Network for Treatment of AIDS)—www.ctu.mrc.ac.uk/penta
PENTA is a collaboration between paediatric HIV centres in Europe, and the site has details of trials, publications, and people to contact

Medscape HIV/AIDS home page—http://hiv.medscape.com/Home/Topics/AIDS/AIDS.html
Offers practice guidelines, conference coverage, continuing medical education (CME) for doctors, and resources for patients.

The tepid response of wealthier nations and private institutions to the newly established Global AIDS and Health Fund is disconcerting. International efforts targeted at HIV infection and AIDS have the potential not only to curb the pandemic but also to galvanise developing countries' governments and flailing health systems into exerting greater energy into eradicating and controlling other common diseases such as tuberculosis and malaria, as well as renewing efforts at community development. Tomorrow's children will judge our resolve or inaction.

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Correction

Infantile colic

In this "Extract from *Clinical Evidence*" by Sally Wade and Teresa Kilgour (25 August, pp 437-40) the number of infants in the five randomised controlled trials looking at the effects of anticholinergic drugs on infantile colic was 134 [not 177] (see last paragraph p 437).

A memorable patient

A question of confidence

She took so long in answering the door and was so breathless when she did so, that I immediately thought that Agnes should be in hospital. A brief chat and examination in her cramped sitting room confirmed that she was in severe left ventricular failure, which had been worsening for nearly a week. I had never met her before, and she was obviously distressed that my partner, who usually sees her, could not come.

"I think we should send for an ambulance to get you into hospital for a few days," I ventured.

Her face froze with fear: "Oh, no. Hospitals are such awful places—noisy, dirty, and, of course, you read about so many mistakes being made and old people being so badly treated nowadays." She wouldn't hear of it.

Sadly, this has been a common enough reaction from older patients in my experience for a long time. What followed, however, was completely new to me.

"Never mind then, we'll try an injection of some medicine instead to get all this fluid off your lungs." I was already reaching for the ampoule when the look of horror flashed over her for a second time.

"Isn't there a tablet I can have instead, doctor?"

I seemed to read her mind and thought I could see her reading mine. "Well, I could give you the same medicine in tablets. Have you got anyone who can get it for you quickly?" (I do not usually carry frusemide tablets with me).

Her nephew was on his way, and she was expecting him in about 20 minutes, so I left her with the prescription. The next day her regular doctor went in to review her and told me she was much better.

But I was not. Though his name was never mentioned, I was deeply troubled that Agnes might have worried that I could be another Harold Shipman when I wanted to inject her. Months later, I was still wondering if I wanted to carry on practising in a so called health service where elderly patients are not only alarmed by the standard of care they assume they will get in hospital but now also fear that any general practitioner they have not seen before cannot be trusted to give them an injection. What a sad commentary on the current climate in which we practise.

As the Elijah mood grew upon me, I thought that this would make a good story for the *BMJ*. But first it was essential to find out if my hunch had been correct. My longsuffering partner agreed to visit Agnes once more and ask her about it. "Oh, no," she smiled, "I've always had a mortal fear of needles. That was all."

But, of course, it wasn't quite all. Though delighted to discover my interpretation of events was unfounded, I remain unsettled by this episode. It shows that, even though Shipman's legacy may not have destroyed the confidence of my patients in me, it has substantially reduced my confidence in treating them.

Trevor Stammers *general practitioner, London*

We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk. Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.